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# A novel solvent-assisted domino Michael-aldol reaction of acenaphthenequinone with acetophenones†

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**Reaction of acenaphthenequinone with acetophenone in methanol in the presence of KOH provides a highly substituted dispiro compound in good yields arising through a novel three-component Michael-aldol domino reaction.**

The efficiency of organic reactions is recognised as an important problem and a domino reaction sometimes provides a fascinating solution.[1] Combining more than one reaction in one flask usually provides better yield and the chance for reactive but not-easy-to-generate and isolate intermediates to be used in the synthetic sequence. Michael addition[2] and aldol reactions[3] are acknowledged as useful tools for constructing complex organic molecules, and combining these two reactions in one flask has been of interest in current organic synthesis. Here, we report a novel domino reaction of acenaphthenequinone with acetophenones in methanol that involves aldol and Michael reactions leading to the formation of a highly substituted dispiro compound. Dispiro compounds are interesting synthetic targets due to their presence in many important natural products.[4]

Base-catalysed aldol condensation of acetophenone with 1,2-diketones such as benzil yields the corresponding α,β-unsaturated ketones[5] as stable products. Similarly, the base-catalysed reaction of benzil with dibenzylketone in methanol yields tetraphenylcyclopentadienone.[6] We have now observed that the reaction of acenaphthenequinone with a slight excess of acetophenone in methanol in the presence of KOH gives a colourless amorphous product. The product showed a broad band at 3345 $cm^{-1}$ in the IR spectrum, indicating the presence of a hydroxy group. In addition, two peaks were observed at 1711 and 1678 $cm^{-1}$. The peak at 1711 $cm^{-1}$ is ascribed to an indenone-type carbonyl.

In the $^1H$ NMR spectrum, four singlets were observed at $\delta$ 2.84 (3H), 5.67 (1H), 6.11 (1H, $D_2O$-exchangeable), and 6.23 (1H) , along with other signals attributable to aromatic protons. In the $^{13}C$ NMR spectrum, thirty-five signals were observed in the range of $\delta$ = 60–209. The signals observed at $\delta$ 197.9, 205.2, and 208.7 are attributed to carbonyl carbons. Signals due to aromatic carbons were observed in the region $\delta$ = 120–143 (26 signals). The attached proton test indicated that three of the carbons appearing in the $\delta$ 60–92 region are attached to either zero or two hydrogens while the remaining three are attached to one or three hydrogens. Based on these data, the compound was identified as the dispiro derivative **6a**. Mass spectral data and elemental analysis are in agreement with the proposed structure.

Similarly, dispiro compounds **6b** and **6c** were synthesised by the reaction of acenaphthenequinone with 4-methylacetophenone and 4-chloroacetophenone, respectively.

Since diffraction-quality crystals of **6a–c** could not be obtained, we carried out energy minimisation studies to determine their lowest energy configurations.[7] The computer-generated 3D structure of **6a** is shown in Fig. 1. We employed the molecular modeling program CERIUS2 (MSI, USA) using COMPASS force field calculation for energy minimisation. Among the various possible diastereomers, the isomer having the *syn* arrangement of two acenaphthenone units appears to be of lowest energy. Furthermore, the unusual upfield shift of the methoxy protons in **6a–c** to around $\delta$ 2.80 is attributable to the positioning of the methoxy group right above the acenaphthenone moiety as observed in the energy-minimised structure of **6a**.

In order to genaralise this novel domino reaction, we attempted the reaction of acenaphthenequinone (**1**) with propiophenone and 2-acetylpyridine (**2d**) under the conditions described above. While propiophenone did not react with acenaphthenequinone even upon prolonged exposure, 2-acetylpyridine reacted slowly to give the corresponding dispiro compound **6d** in moderate yields.

A possible mechanism for the formation of **6** involving a dibenzoylalkene-type intermediate **3**[8] is given in Scheme 1. The initial condensation between acenaphthenequinone (**1**) and acetophenone (**2**) gives the acenaphthenone-2-ylidene ketone **3**, which undergoes Michael-type addition with a molecule of methanol to give the intermediate **4**. Michael addition of **4** to another molecule of **3** followed by cyclisation yields **6**. Though the analogous Michael addition reaction of

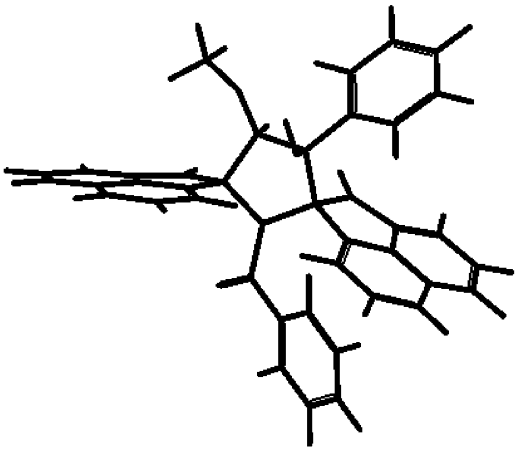
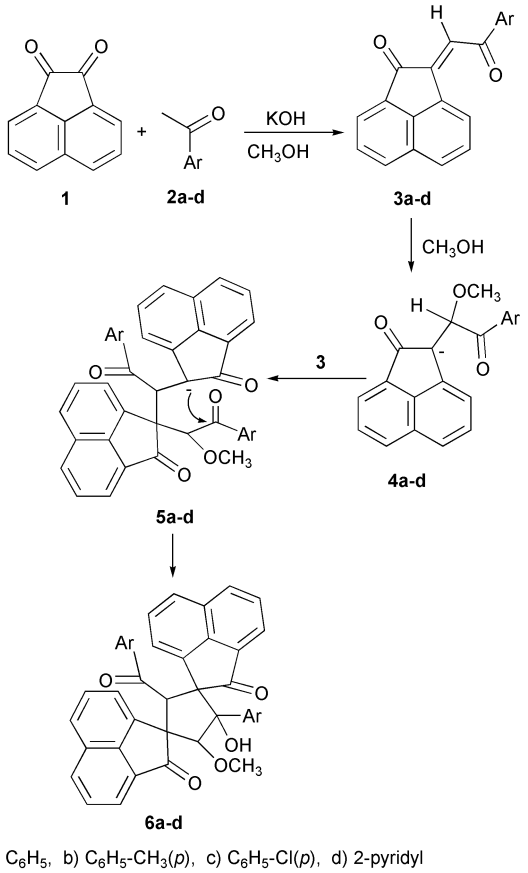


**Fig. 1** Energy minimised structure of dispiro compound **6a**.

† Electronic supplementary information (ESI) available: $^1H$ and $^{13}C$ NMR spectra for **6a–c**. See http://www.rsc.org/suppdata/nj/b2/b202454c/




**Scheme 1**

*trans*-dibenzoylalkenes with acetophenones resulting in the formation of highly substituted cyclohexanol derivatives is reported in the literature,[9] our findings represent the first observation of the solvent-assisted dimerisation of dibenzoylalkene-type systems. The driving force behind this domino process is probably the *o*-quinonemethide-like structure of acenaphthenone-2-ylidene ketones **3a–d**, which makes them excellent Michael acceptors.

In summary, the reaction of acenaphthenequinone and acetophenones described herein provides a simple and direct entry into a number of interesting novel dispiro compounds in good yields by the domino Michael-aldol reaction. A putative mechanism involving base-catalysed aldol condensation followed by dehydration, solvent addition and Michael addition reactions rationalises the formation of the dispiro compounds. Further investigations to explore the scope and mechanistic underpinnings of the reaction are in progress.

## Experimental

### General methods

Acenaphthenequinone (purity >98%) and acetophenones (purity >97%) were used as supplied (E. Merck). Solvents were distilled before use. The $^1$H and $^{13}$C NMR spectra were recorded at 400 and 500 MHz on a Bruker FT-NMR spectrometer or GE NMR OMEGA spectrometer with tetramethylsilane as internal standard. All melting points are uncorrected and were determined on a Neolab melting point apparatus. Infrared spectra were recorded using a Shimadzu-DR-8001 series FTIR spectrophotometer. Mass spectra were recorded on a Finning MAT 1020 mass spectrometer operating at 70 eV. Elemental analysis was performed at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow.

### Typical synthetic procedure

A mixture of acenaphthenequinone (4.6 g, 25 mmol), acetophenone (3.2 g, 27 mmol), and powdered potassium hydroxide (1.0 g) in methanol (30 mL) was stirred at about 60 °C for 12 h and then kept in a refrigerator for 48 h. The solid product that separated out was filtered and purified by recrystallisation from a mixture (2:1) of methanol and dichloromethane to give **6a**.

**Spectral data for 6a.** Yield 4.0 g (47%); mp > 250 °C; IR $\nu_{max}$ (KBr) 3345 (OH), 1711 and 1678 (C=O) cm$^{-1}$; UV $\lambda_{max}$ ($CH_3CN$) 215 ($\varepsilon$ 44 000), 248 ($\varepsilon$ 15 000), 341 nm ($\varepsilon$ 4600 cm$^2$ mol$^{-1}$); $^1$H NMR ($CDCl_3$) $\delta$ 2.84 (s, 3H, $OCH_3$), 5.67 (s, 1H), 6.11 (s, $D_2O$-exchangeable, 1H), 6.23 (s, 1H), 6.60–8.50 (m, 22H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$ 60.3 ($OCH_3$), 63.6 (C), 65.2 (CH), 70.0 (C), 84.0 (C), 91.2 (CH), 120.8 (CH), 123.0 (CH), 123.9 (CH), 124.2 (CH), 125.1 (CH), 125.4 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.4 (CH), 128.8 (CH), 129.8 (CH), 130.6 (C), 131.2 (CH), 132.2 (CH), 133.0 (C), 133.1 (CH), 134.8 (C), 136.5 (C), 138.0 (C), 138.3 (C), 140.6 (C), 142.2 (C), 142.7 (C), 197.9 (C=O), 205.2 (C=O), 208.7 (C=O); EI MS $m/z$ 582 $(M-H_2O)^+$. Anal. calcd for $C_{41}H_{28}O_5$: C, 81.98; H, 4.70; found: 81.71; H, 4.77.

**Spectral data for 6b.** Yield 4.7 g (60%); mp > 250 °C; IR $\nu_{max}$ (KBr) 3348 (OH), 1711, and 1676 (C=O) cm$^{-1}$; UV $\lambda_{max}$ $CH_3CN$) 215 ($\varepsilon$ 42 000), 251 ($\varepsilon$ 16 000), 341 nm ($\varepsilon$ 4600 cm$^2$ mol$^{-1}$); $^1$H NMR ($CDCl_3$) $\delta$ 1.92 (s, 3H, $CH_3$) 2.05 (s, 3H, $CH_3$), 2.82 (s, 3H, $OCH_3$), 5.63 (s, 1H), 6.03 (s, $D_2O$-exchangeable, 1H), 6.21 (s, 1H), 6.40–8.50 (m, 20H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.0 ($CH_3$), 21.3 ($CH_3$), 60.2 ($OCH_3$), 63.6 (C), 64.9 (CH), 69.8 (C), 84.6 (C), 91.1 (CH), 120.8 (CH), 122.5 (CH), 123.4 (CH), 124.1 (CH), 124.6 (CH), 124.9 (CH), 126.8 (CH), 127.2 (CH), 122.8 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 129.6 (CH), 130.2 (C), 130.3 (C), 130.9 (CH), 132.5 (CH), 132.9 (C), 133.7 (C), 134.6 (C), 134.8 (C), 136.8 (C), 138.0 (C), 140.5 (C), 142.1 (C), 142.5 (C), 142.7 (C), 197.2 (C=O), 205.4 (C=O), 208.3 (C=O). EI MS $m/z$ 610 $(M-H_2O)^+$. Anal. calcd for $C_{43}H_{32}O_5$: C, 82.15; H, 5.13; found: 82.18; H, 5.19.

**Spectral data for 6c.** Yield 3.8 g (45%); mp > 250 °C; IR $\nu_{max}$ (KBr) 3341 (OH), 1707, and 1682 (C=O) cm$^{-1}$; UV $\lambda_{max}$ ($CH_3CN$) 218 ($\varepsilon$ 39 000), 251 ($\varepsilon$ 14 000), 341 nm ($\varepsilon$ 4000 cm$^2$ mol$^{-1}$); $^1$H NMR ($CDCl_3$) $\delta$ 2.80 (s, 3H, $OCH_3$), 5.57 (s, 1H), 5.94 (s, $D_2O$-exchangeable, 1H), 6.13 (s, 1H), 6.50–8.10 (m, 20H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$ 60.3 ($OCH_3$), 63.4 (C), 65.0 (CH), 69.7 (C), 84.3 (C), 90.9 (CH), 121.2 (CH), 123.0 (CH), 123.5 (CH), 124.1 (CH), 125.0 (CH), 125.3 (CH), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.6 (CH), 130.3 (C), 130.4 (CH), 131.3 (CH), 132.6 (C), 133.1 (CH), 133.4 (C), 134.2 (C), 134.5 (C), 136.4 (C), 137.1 (C), 138.3 (C), 140.0 (C), 142.0 (C), 142.4 (C), 196.4 (C=O), 205.2 (C=O), 208.0 (C=O). Anal. calcd for $C_{41}H_{26}O_5Cl_2$: C, 73.55; H, 3.91; found: 73.77; H, 4.04.

**Spectral data for 6d.** Yield 2.0 g (26%); mp > 250 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.77(s, 3H, $OCH_3$), 5.30 (s, 1H), 5.96 (s, 1H), 6.30 (s, 1H), 6.60–8.60 (m, 20H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$ 60.5 (s, 3H, $OCH_3$), 63.5, 66.0, 68.6, 86.7, 91.6, 121.0, 122.4, 123.1, 123.2, 123.6, 124.1, 124.5, 125.8, 127.6, 128.2, 129.1, 129.2, 130.0, 130.2, 131.4, 131.9, 134.1, 135.2, 135.6, 135.9, 137.7, 141.3, 141.5, 142.4, 146.7, 197.1, 204.3, 208.8.

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